REMARKS

This application has been amended in a manner to place it in condition for allowance.

Status of the Claims

Claim 15 is amended. Support for the amendment to the claims may be found, for example, in the second from the last paragraph of page 24 of the originally filed specification.

Claims 15-34 are pending in this application.

Claims 15-19, 23-25 and 29-32 were examined on the merits and stand rejected.

Claims 20-22, 26-28, 33, and 34 were withdrawn as non-elected subject matter.

Information Disclosure Statement

The Non-patent literature cited in the IDS of June 25, 2009 were not considered because an English translation or English abstract was not included.

However, a concise explanation of relevant sections of these documents were translated, e.g., designated by the circled sections or “side”. See, for example, the last pages of the non-English language documents.

Thus, consideration of is respectfully requested.

Claim Rejections-35 USC §103

Claims 15-18, 23, 24, 29, and 30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over PARK et al. Bone, 1999, 24: 549-554 (PARK) in view of both LECOEUR et al. Biomaterials, 1997, 18: 989-993(LECOEUR) and SUGIHARA et al. Differentiation, 1986, 31:42-49(SUGIHARA). This rejection is respectfully traversed for the reasons that follow.

PARK was offered for teaching isolating, cultivating, and cloning mature adipocytes from human bone marrow; the cloned mature adipocytes are further cultured and dedifferentiated to fibroblast-like fat cells (i.e., pre-adipocytes), wherein the pre-adipocytes do not have lipid droplets and wherein the pre-adipocytes express alkaline phosphatase.

The Official Action recognized that PARK fails to teach deriving pre-adipocytes from the dedifferentiation of mature adipocytes isolated from subcutaneous fat tissue, nor do they teach ceiling culture.

SUGIHARA was offered for teaching such a method.

However, SUGIHARA fails to remedy the deficiencies of PARK for references purposes.

SUGIHARA discloses that after unilocular adipocytes (mature adipocytes) are subjected to ceiling culture, the unilocular adipocytes (mature adipocytes) are morphologically changed to (i) multilocular adipocytes having many small lipid

droplets in their cytoplasms or (ii) fibroblast-like adipocytes having minute lipid droplets in their cytoplasms. However, SUGIHARA requires establishing a long-term culture system of adipocytes as each of the adipocytes maintains its specific functions as adipocytes. As described above, SUGIHARA has only disclosed a system capable of culturing adipocytes over the long term in a state where the functions of the adipocytes are maintained. Thus, the preadipocytes of the claimed invention would have been difficult to provide by the method of SUGIHARA. In fact, SUGIHARA fails to suggest that preadipocyte cell line is obtained from dedifferentiated adipocytes.

When the International Application of the present National Stage Application was filed, there were neither articles proving that a once terminally differentiated somatic cell obtained prior to the stage of a precursor cell, and further, obtained prior to the stage of a pluripotent precursor cell, nor such an idea. Instead, only a method of subjecting a terminally differentiated cell to nuclear transplantation into an enucleated unfertilized egg was known, and there was no suggestion that a preadipocyte could be obtained from a terminally differentiated adipocyte by continuing the culturing of adipocyte. Even today, the data supporting the claimed invention (as described in the originally filed International Application) is unique. Articles presenting main data for the idea passed peer review in November,

2009 and will be published in Journal of Cellular Biochemistry (see the appendix).

In the method of SUGIHARA, unilocular adipocytes are subjected to ceiling culture, and the culturing of the unilocular adipocytes is further continued in a manner in which the cell adhesion surface is the bottom surface. However, SUGIHARA fail to clearly disclose, unlike amended independent claim 15, "continuing culturing of cells in a form of a fibroblast having no lipid droplets at all in a manner in which a cell adhesion surface is a bottom surface after a stage where a large number of the cells are observed".

In addition, SUGIHARA further fails to disclose that after obtaining fibroblast-like adipocytes having no lipid droplets in their cytoplasms, the fibroblast-like adipocytes are further subjected to passage culture to induce dedifferentiation, and, consequently, obtaining fibroblast-like preadipocytes, which all have no lipid droplets in their cytoplasms and have no function specific to adipocytes. The preadipocyte cell line of the claimed invention is obtained through the above-mentioned process.

In PARK as well, the cells used are contained in floating fractions obtained by subjecting bone marrow aspirates to a centrifugation treatment. However, these cells do not undergo a collagenase treatment and a filtration treatment using meshes having a pore diameter of about 250 μm after the

centrifugation treatment. Thus, one of ordinary skill in the art would have presumed that, according to PARK, cells contaminated with bone marrow stromal cells or the like would be used as adipocytes.

In addition, PARK fails to prove that only adipocytes were collected and cultured, and even admits that S-V fractions were contaminated in the cells. Bone marrow stromal cells are pluripotent cells, and it is obvious that the bone marrow stromal cells are differentiated and induced to adipocytes. Therefore, one of ordinary skill in the art would have concluded that the differentiated cells obtained by PARK had originated from the contaminated bone marrow stromal cells, and hence, it would have been unobvious that that adipocytes would have been used to acquire a differentiation ability.

Moreover, at the time PARK was disclosed, it was outside the accepted notion that terminally differentiated adipocytes were dedifferentiated and used at the stage of precursor cells, let alone that pluripotent cells could be acquired.

Indeed, there is no teaching prior to the present application indicating that pluripotent precursor cells can be acquired from terminally differentiated adipocytes. This is evidenced by the fact that the article written by inventors has been published in multiple international journals with Peer Review since 2008, and hence, the inventors' article is

significantly unique, even at present. As a method utilizing terminally differentiated somatic cells at an early stage, this method of producing iPS cells by introducing Yamanaka factors is attracting attention at present around the globe. However, the preadipocyte cell line of the present invention is a significantly unique cell, because the cell is acquired by inducing dedifferentiation of terminally differentiated adipocytes without using the Yamanaka factors.

The foregoing indicates that the preadipocyte cell line as described in independent claim 15 cannot be acquired by the method described in SUGIHARA, and even the combination of the method described in SUGIHARA with PARK does not allow the adipocytes to be used to obtain preadipocytes.

Therefore, the proposed combination fails to render obvious independent claim 15, and, accordingly, dependent claims 16-18, 23, 24, 29, and 30, and withdrawal of the rejection is respectfully requested.

Claims 15-19, 23-25, and 29-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over PARK taken with LECOEUR and SUGIHARA in view of ROSS (Science, 2000, 289:950-953), BENNETT (J. Biol. Chem., June 7, 2002, 277:30998-31004) and RANDO (J. Cell Biol., 1994, 125:1275-1287). This rejection is respectfully traversed for the reasons that follow.

As mentioned above, PARK fails to teach deriving pre-adipocytes from the dedifferentiation of mature adipocytes

isolated from subcutaneous fat tissue, nor do they teach ceiling culture.

SUGIHARA fails to remedy the deficiencies of PARK for references purposes for the reasons also discussed above.

ROSS, BENNNET, and RANDO also fail remedy these deficiencies of PARK for reference purposes.

ROSS and BENNETT prove that the signaling of Wnt10b is important for deciding the destiny of a mouse embryo-derived preadipocyte cell line and myoblast cell line. However, Wnt10b is not additionally used for inducing differentiation of the preadipocyte of the claimed invention to a myoblast. Moreover, it would have been unexpected for one of ordinary skill in the art to categorize, in the same group, a preadipocyte cell line established by cloning a fibroblast of a fetal mouse of about 13 days old from viviparity in which an fat tissue is not yet formed at all and a preadipocyte cell line established by culturing a terminally differentiated adipocyte and inducing dedifferentiation of the adipocyte. The reasons one would not have categorized these preadipocyte cell lines in the same group follow.

A preadipocyte cell line used for inducing transdifferentiation in the claimed invention is a pluripotent precursor cell obtained by culturing a terminally differentiated adipocyte and inducing dedifferentiation of the adipocyte and is an artificially produced (pluripotent) cell. The above fact

indicates that the preadipocyte cell line is an artificial cell similar to an iPS cell obtained under an artificial environment by introducing Yamanaka factors into a terminally differentiated gastric mucosal epithelium or a terminally differentiated hepatocyte, and, accordingly, the preadipocyte cell line is considered to be a novel pluripotent precursor cell. Such a cell does not exist in an organism, and, thus, such a cell is outside the cell lineage (differentiation process) of from a stem cell to a differentiated cell via a precursor cell, as disclosed by ROSS and BENNETT.

It has certainly been proven that the mouse precursor cell line along the cell lineage has a pathway of differentiation to a myocyte with the addition of Wnt10b. However, it is not always certain that a preadipocyte cell line outside the cell lineage, i.e., that of the claimed invention, follow a similar pathway, and it is not always certain that the addition of Wnt10b induces the differentiation of the preadipocyte cell line to a myocyte. In fact, in the mouse preadipocyte (in the state where no Wnt10b is added) described in ROSS and BENNETT, the expression of the MyoD gene, which is a master regulator of differentiation to a skeletal muscle, is not observed, and the addition of Wnt10b induces the expression, shifting to the lineage of differentiation to a muscle. In the present invention, expression of MyoD is observed before the induction of differentiation (FIGS. 9. 11), and hence, it is reasonably

thought that the preadipocyte of the present invention must have a pathway different from that of the mouse preadipocyte described in ROSS and BENNETT.

Moreover, in the claimed invention, the differentiation of the preadipocyte to a myoblast can be induced without the addition of Wnt10b. Accordingly, the claimed invention as described in independent claim 15 and dependent claims 16-19, 23-25, and 29-32, is not is not obvious because it is not taught by the combination of LECOEUR, SUGIHARA, and PARK and additionally, ROSS, BENNETT, and RANDO.

Moreover, the inventors have revealed that during the process of obtaining the preadipocyte cell line, a group of genes having a function of inhibiting the action of Wnt is highly expressed in the step of dedifferentiation from an adipocyte (in an article under publication). The fact indicates that the system of Wnt will not be activated in the preadipocyte cell line.

Therefore, withdrawal of the rejection is respectfully requested.

Claims 15-18, 23, 24, 29 and 30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over PARK in view of LECOEUR and KANO et al. JP2000-083656 (KANO). This rejection is respectfully traversed for the reasons that follow.

As discussed previously, PARK fails to teach deriving pre-adipocytes from the dedifferentiation of mature adipocytes

isolated from subcutaneous fat tissue, nor do they teach ceiling culture.

The preadipocyte described in independent claim 15 is obtained by a method similar to that in KANO and has properties similar to that of the preadipocyte of KANO. As described in PARK, it is not easily accomplished to induce transdifferentiation of the preadipocyte cell line to a cell having other functions.

The preadipocyte cell line of the present invention is, as described above, a unique artificial cell obtained by causing a terminally differentiated mature adipocyte previously obtained under an artificial environment in the same way as the iPS cell.

The preadipocyte cell line of the present invention described above has the following characteristics. In view of the situation in the progress of studies on the field to which the present invention pertains at the time the invention was made, it would not have easily been presumed, as described above, that even if the induction of transdifferentiation of the preadipocyte cell line was performed based on the descriptions of PARK and LECOEUR, it was not known whether the preadipocyte cell line would undergo the transdifferentiation to a cell having other functions. Therefore, the present invention is novel even at present because, for example, the invention has recently been published in an international journal.

The fact that the present invention has induced the differentiation of the preadipocyte cell line having the utility described below to a cell having other functions is very useful in the technical development and exerts a remarkable effect.

Should the Examiner require this description in the form of declaration under 37 CFR 1.132, the inventors kindly request that the Examiner notify the undersigned.

Preadipocyte cell line of present invention and utility of induction of differentiation of preadipocyte cell line

1) The present invention has found for the first time that a preadipocyte cell line, which can be cultured by long-term passage culture, is stable, and has unique properties even though the cell is derived from a terminally differentiated mature adipocyte, can provide various cells having other functions, such as an adipocyte, an osteoblast, a myocyte, a chondrocyte, and further, across different germ layers, a neurocyte and an epithelial cell.

It was said at a time when the invention of the subject application was filed that the technical level should not have provided pluripotency (that is, property of differentiating to a cell having other functions) similar to that of an ES cell or MSC to a cell obtained by just using a terminally differentiated cell and merely devising the culture method.

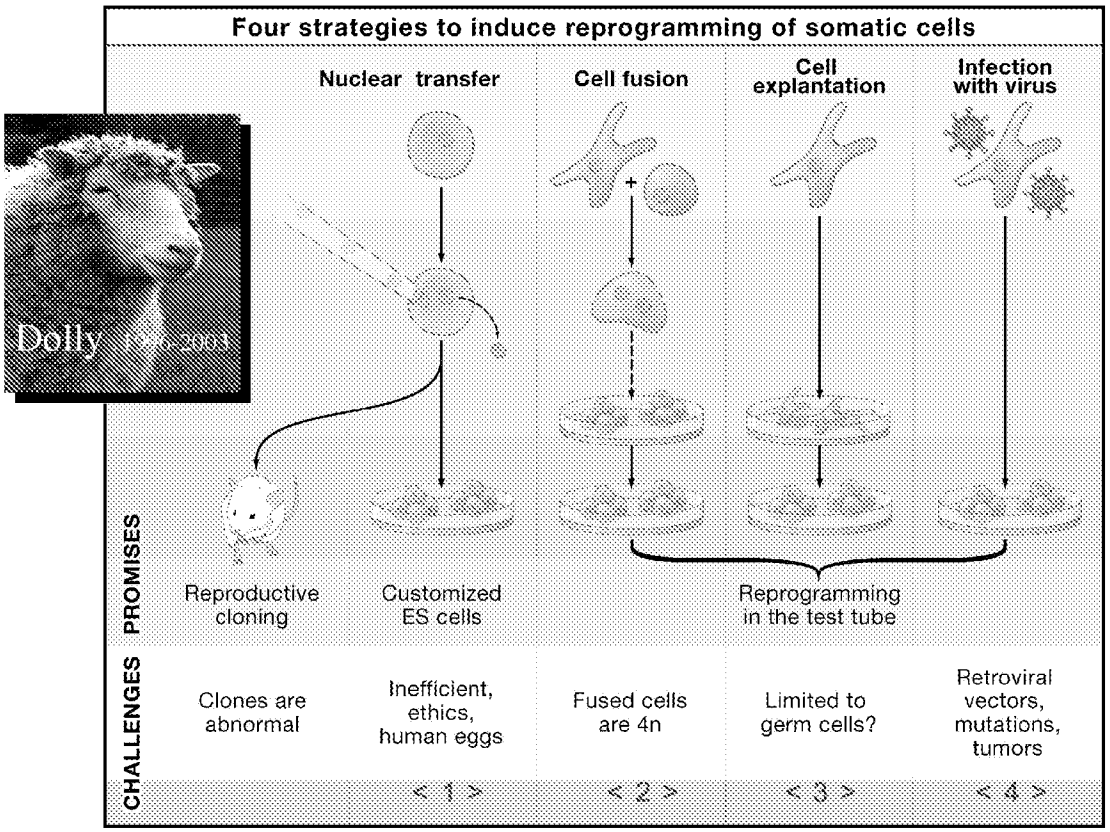
The following four methods are known at present as methods of producing a pluripotent cell capable of differentiating to a cell having other functions from a terminally differentiated somatic cell (See Figure 1 below). However, any of the methods requires the use of the ability of an intrinsically pluripotent oocyte or an intrinsically pluripotent ES cell or introduction of an exogenous gene, and it is thought to be difficult even at present to obtain by just using a terminally differentiated cell and merely devising the culture method.

In contrast, the inventors of present application have been successful in obtaining the preadipocyte cell line of the present invention merely by the device of the culture method, in which terminally differentiated mature adipocytes (unilocular adipocytes) are subjected to ceiling culture, the culture is further continued in a manner in which a cell adhesion surface is a bottom surface after a stage where a large number of the cells in a form of a fibroblast having no lipid droplets at all are observed, to thereby obtain fibroblast-like adipocytes having no lipid droplets in cytoplasms, and the fibroblast-like adipocytes having no lipid droplets in cytoplasms are subjected to passage culture to induce dedifferentiation.

The above-mentioned technique could not have easily been foreseen even by those skilled in the art, not to mention, when the invention was made.

Therefore, the present invention in which a preadipocyte cell line derived from a terminally differentiated cell is used to acquire a cell having other functions was an epoch-making invention at the time of its filing and even at present.

Figure 1: Method of producing pluripotent cell from somatic cell



<1> Technique of producing somatic cell clone by using the reprogramming ability of an oocyte, a nucleus of a somatic cell is injected into an enucleated oocyte under microscope to initialize the nucleus of a somatic cell, to thereby produce a pluripotent cell (egg).

<2> By using the reprogramming ability of an ES cell instead of that of an oocyte in the above item <1>, an ES cell and a somatic cell are fused to give an initialized cell, to thereby produce a pluripotent cell.

<3> By bringing an Es cell into contact with a somatic cell, the ES cell and the somatic cell are cocultivated, to thereby produce a pluripotent cell.

<4> Specific genes (Yamanaka factors) are introduced into a virus, a somatic cell is infected with the virus, and the genes are overexpressed to initialize the somatic cell, to thereby produce a pluripotent cell.

2) As pluripotent cells, known at present are an embryonic stem cell (ES cell), somatic stem cells including a hematopoietic stem cell (hereinafter referred to as HSC), an MSC, an fat tissue-derived stem cell (hereinafter referred to as ASC), and a myoblast, and a cord blood stem cell and an iPS cell. Various studies are underway for utilizing those cells as cell sources for regenerative medicine.

The cell source for regenerative medicine ideally has the following properties:

- The cells are applicable to autologous transplantation and allogeneic transplantation (cell bank).
- Minimally-invasive cell collection is possible.
- The cells can be easily proliferated.
- The cells can be safely transplanted (highly pure and homogeneous cells can be transplanted and the cells lack oncogenicity).

Those pluripotent cells, however, have the advantages and disadvantages listed in Table 2 below, and hence, those are not particularly suitable cells as the cell sources for regenerative medicine.

Table 2: Advantages and disadvantages as cell sources for regenerative medicine

	Advantages	Disadvantages
ES cell	Pluripotent Easily proliferating	Ethical and religious problems exist. Only allogeneic transplantation is possible. Malformed species exist.
Somatic stem cell	Autologous transplantation is possible. Lacking oncogenicity	Not pluripotent Cell collection involves invasion. The cell is difficult to collect from the elderly and children. The cell group has low purity.
Cord blood stem cell	Minimally invasive	Only allogeneic transplantation is possible. The number of cells is small (difficult proliferation). Not pluripotent
iPS cell	Pluripotent Autologous transplantation is possible. No ethical and religious problems exist.	Exerting oncogenicity To establish the cell, a virus vector is used for gene introduction. Low in inductive efficiency

In contrast, the preadipocyte cell line of the present invention of the subject application has been confirmed to have the following characteristics, and hence, the preadipocyte cell line is a desirable cell as a cell source for regenerative medicine, compared with the above-mentioned cells.

<Characteristics of preadipocyte cell line>

- Autologous transplantation is easily possible.
- Cell collection involves a low degree of invasion compared with a bone marrow mesenchymal stem cell.

- An extremely low amount of other cells is contaminated compared with a bone marrow mesenchymal stem cell and an adipose-derived mesenchymal stem cell, and the cell line is low in risk associated with transplantation.
- The cell line can be collected even from the elderly and newborn infants whose bone marrow is difficult to collect, and has pluripotency irrespective of the age of donors (Table 3 and Figure 2).
- The cell line can be easily prepared in large amount from a small amount of subcutaneous fat tissue.
- Banking using fat tissue that is disposed during operation is possible, and the application to allogeneic transplantation is promising (In allogeneic transplantation, the immunity problem must be taken into consideration, and thus, bone marrow transplantation and cord blood transplantation require matching of total 6 types of HLAs, that is, HLA-A, HLA-B, and HLA-DR multiplied by 2 at MHC. Accordingly, marrow transplantation is said to need 300,000 donor registrations. The preadipocyte cell line does not express HLA-DR, and hence, matching of total 4 types of HLAs, that is, HLA-A and HLA-B multiplied by 2, is necessary, resulting in an overwhelmingly small number of their combination, one tenth of that for marrow transplantation).

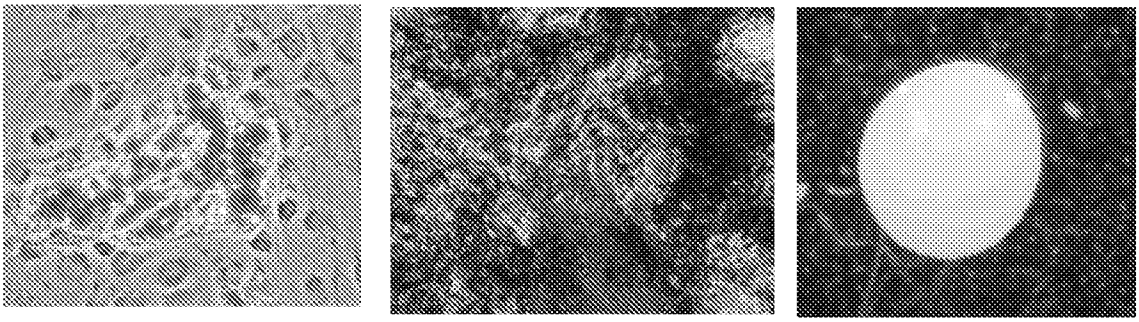
- Passage culture as long as 30 passages or more is possible, and the cell has high proliferation activity (doubling time 65 hours).
- The cell at the clone level exerts pluripotency to bone, cartilage, adipocyte, or the like.
- The cell has, in vitro and in vivo, pluripotency to a vascular endothelial cell, a smooth muscle cell, a cardiomyocyte, or the like.
- The cell expresses and secretes cytokines such as MCP-1, IL-6, IL-8, TMP-1, TMP-2, TGF-β, HGF, and VEGF.

Table 3: The pluripotency irrespective of the age of donors

Age of donors	Sex	Passage number	Differentiation to adipose tissue	Differentiation to osseous tissue	Differentiation to cartilaginous tissue
2	F	P3	+	+	+
4	M	P5	+	3+	+
7	M	P5	+	2+	+
10	M	P3	±	+	+
10	M	P8	+	+	+
16	M	P4	2+	3+	+
46	F	P7	+	3+	+
58	F	P4	2+	2+	+
68	M	P4	2+	+	+
69	F	P6	+	+	+
75	F	P3	2+	2+	+
77	F	P2	3+	3+	+
81	M	P3	2+	2+	+

Differentiation instruction four days later
Differentiation to adipose tissue (Oil red-O), Differentiation to osseous tissue (ALP stain, Alizerin-red S), Differentiation to cartilaginous tissue (Pellet culture, Aggrecan stain)

Figure 2: Differentiation example of preadipocyte cell line derived from mature adipocyte from donor of 81 years old



(Oil red-O) (Alizerin-red S) (Pellet culture, Aggrecan stain)

3) Difference between preadipocyte cell line and iPS cell.

The preadipocyte cell line resembles the iPS cell in the point that mature cells abundant in living organisms are processed to obtain undifferentiated cells.

However, as illustrated in Figure 3 below, the iPS cell is a cell obtained by introducing four genes into a mature cell and recovering it (performing reprogramming) up to the level of the embryonic stem cell, whereas the preadipocyte cell line is a cell obtained by dedifferentiating a mature cell up to the level of the mesenchymal progenitor cell by simpler ceiling culture.

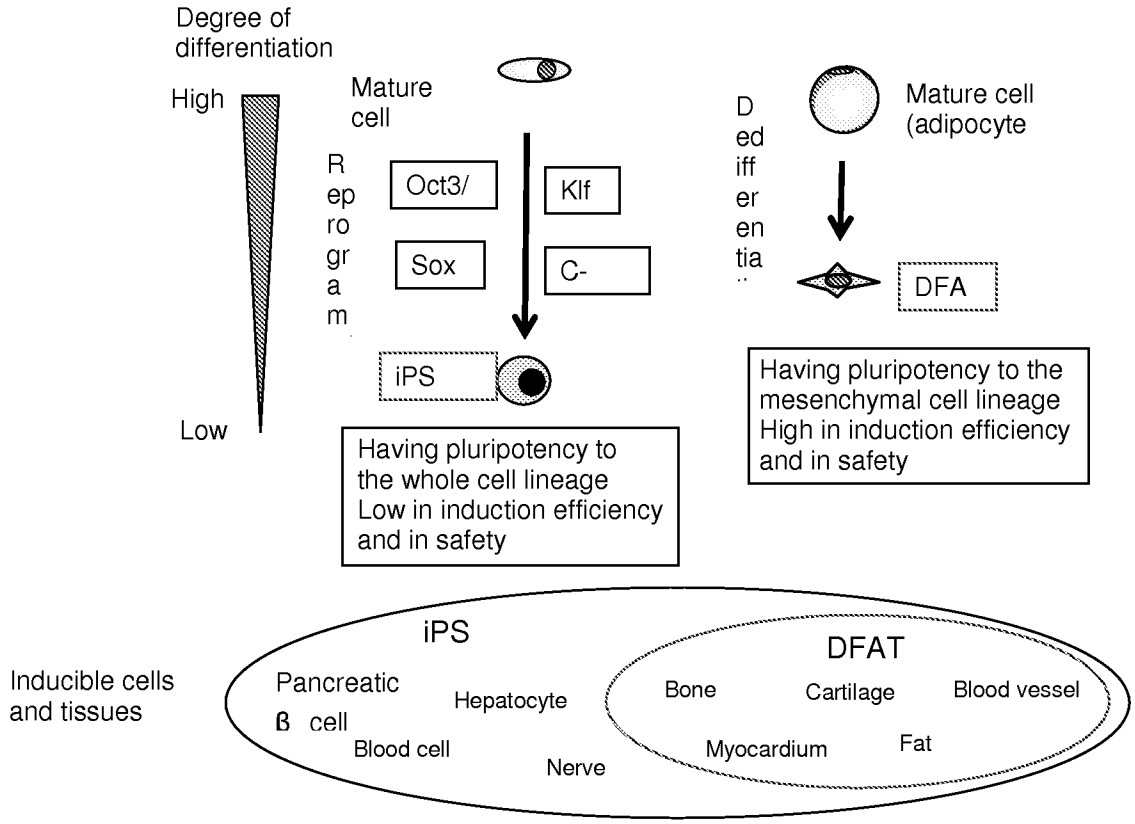
Thus, the preadipocyte cell line has pluripotency to mesodermal tissue such as bone, cartilage, fat, blood vessel, or myocardium, but has a disadvantage that the cell line has no differentiation potency to the whole cell lineage unlike the iPS cell.

However, the iPS cell has many problems in that the

cell has tumorigenicity because it is a highly undifferentiated cell, the cell lacks safety because of gene introduction and use of a virus vector, it takes a long time to establish the cell, establishment of the cell lacks efficiency, and the like. Further, the induction efficiency of the iPS cell from the mature cell of adults, particularly from the mature cell of the elderly is very low, and hence, it is expected that it will take a long time to develop the iPS cell as a cell for autologous transplantation.

In contrast, the preadipocyte cell line is a cell high in degree of differentiation and low in tumorigenicity, and is highly safe because the preparation of the cell line does not require special operations such as gene introduction. Further, the cell line can be prepared even from a cell of the elderly efficiently in a short time. Thus, the preadipocyte cell line is a desirable cell as a cell source for regenerative medicine compared with the iPS cell, and its earlier clinical applications can be expected.

Figure 3: Difference between preadipocyte cell line and iPS cell



4) Difference between preadipocyte cell line and MSC·ASC

MSC and ASC are somatic stem cells present in living organisms in small amount and have high proliferative capacity and pluripotency to mesodermal tissue.

MSC can be obtained by collecting bone marrow aspirates through bone marrow aspiration and subjecting the bone marrow aspirates to adherent culture in a culture dish, to thereby proliferate the aspirates, and has been confirmed to be almost free of oncogenicity. Further, clinical testing of MSC for autologous cell transplantation has started in the area of bone,

cartilage, myocardium, and the like. ASC is a cell group obtained by performing liposuction under general anesthesia and subjecting stroma fractions obtained by removing mature adipocytes from the sucked fats to adherent culture, to thereby proliferate the stroma fractions.

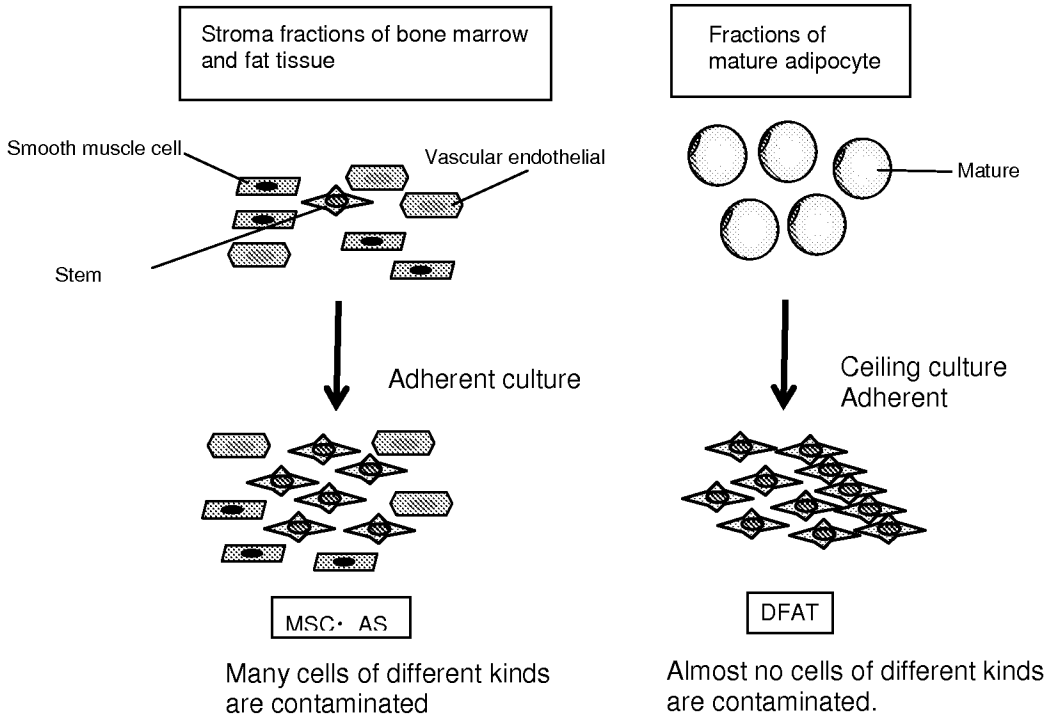
Both MSC and ASC have problems in that (1) there are cases where their collection is impossible, such as collection from the elderly, and (2) adherent culture is performed under the condition where various cell groups are contaminated, and hence, contamination of other cells is inevitable. The inventors of the subject application have analyzed the cell surface antigens of MSC and ASC, and as a result, have confirmed that 13 to 19% smooth muscle myoblasts and 2 to 5% vascular endothelial cell were contaminated at the time of the primary culture of ASC. The foregoing is a critical problem under the circumstances where standardization of cells for transplantation is demanded.

To cope with the above problem, processing for providing highly purified ASC is performed by increasing the passage number at present, but it has been revealed that the processing causes reduction in proliferative capacity and differentiation potency of ASC.

On the other hand, the preadipocyte cell line has advantages in that (1) collection of 1 g of fat tissues under local anesthesia results in preparation of the cell line, and hence, the collection involves a very low degree of invasion and

tissue destruction, and collection of fat tissues even from patients whose systemic condition is in malfunction, such as a patient of severe cardiac failure, is possible to prepare the preadipocyte cell line, and (2) preparation is possible for any person ranging from the newborn infant to the elderly of 80 or more years old. Further, as illustrated in Figure 4, the preadipocyte cell line has a characteristic in that (3) because mature adipocytes are cultured after isolation, other cells are contaminated to very small extent, and hence, highly purified cells can be obtained even at the time of the primary culture.

Figure 4: Difference between preadipocyte cell line & MSC·ASC



5) Utility of preadipocyte cell line

Since the filing of the invention of the subject application, the inventors have been performing various studies to find applications in regenerative medicine by using the preadipocyte cell line, and have confirmed that the preadipocyte cell line used in the invention of the subject application can be utilized for the clinical application cases described below.

<Transplantation of preadipocyte cell line to injured parts>

The inventors have confirmed that transplantation of the preadipocyte cell line to injured parts exhibits an action of

improving blood flow in the limb ischemia model and an action of improving cardiac function in the myocardial infarction model.

In addition, for example, a method of promoting angiogenesis by transplanting the preadipocyte cell line to the patients of peripheral arterial occlusive disease (PAD) (FIGURE 5), and a method of promoting bone fracture healing by transplanting the preadipocyte cell line (Figure 6) are now under investigation. The inventors have confirmed that the transplantation of the preadipocyte cell line to the patients of peripheral arterial occlusive disease (PAD) is more effective than transplantation of bone marrow monocytes (BM-MNC) (Table 4).

Table 4:
Promotion of angiogenesis in patients of peripheral arterial occlusive disease (PAD)

	Bone marrow monocytes (BM-MNC)	Preadipocyte cell line
Tissue collected	Iliac bone marrow aspirates	Subcutaneous fat tissue
Amount of tissue collected	600 to 800 ml	About 1 g
Anesthesia method	General anesthesia	Local anesthesia
Homogeneity of cells	Low	High
Collection from elderly patients	Impossible	Possible
Collection from patients of osteomyelitis complication	Impossible	Possible
Secretory ability of angiogenic factors	Medium	High
Secretory ability of inflammatory cytokines	High	Medium

Figure 5: Method of promoting angiogenesis by transplanting preadipocyte cell line in patients of peripheral arterial occlusive disease (PAD)

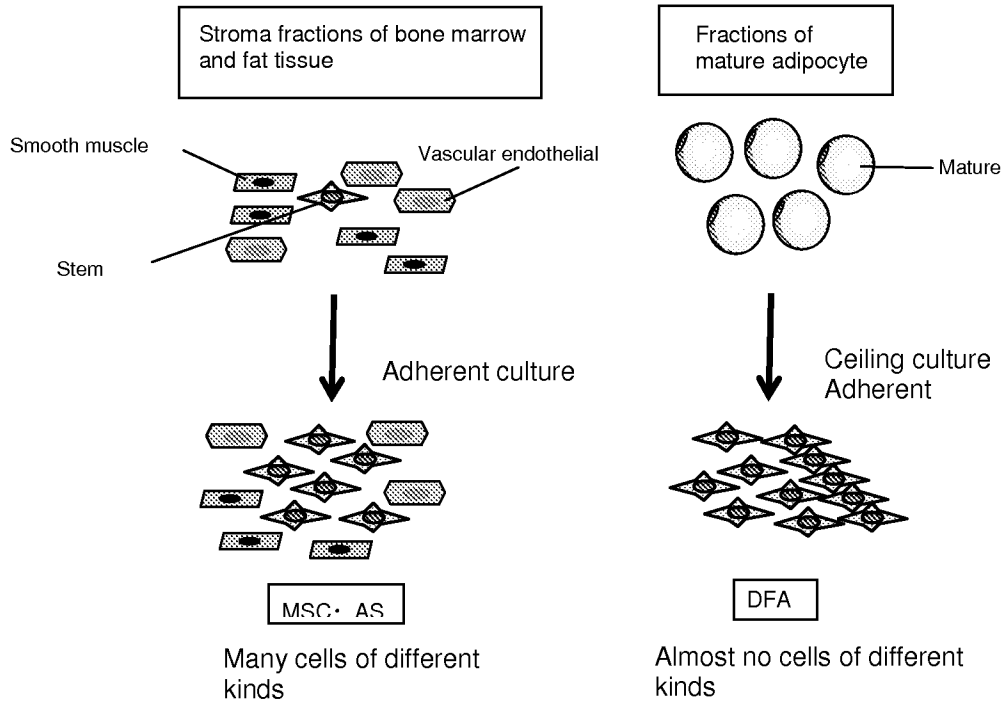
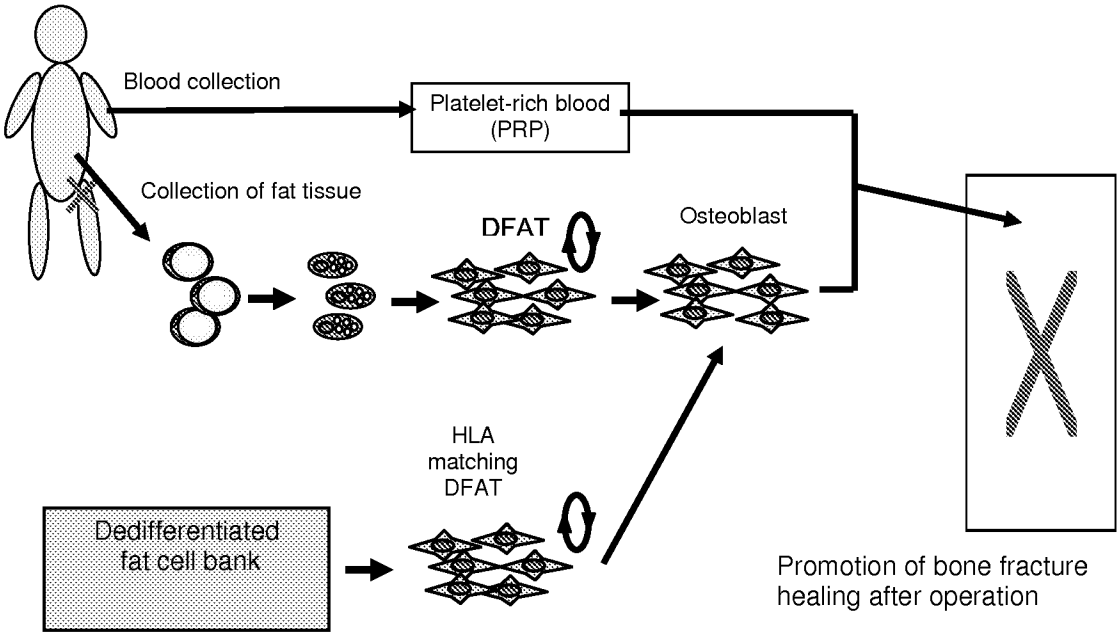


Figure 6: Method of promoting bone fracture healing by transplanting preadipocyte cell line



Further, the inventors prepared a preadipocyte cell line from a GFP mouse to use in experiments, in which the inventors have clarified in both the systems of in vitro and in vivo that the preadipocyte cell line transdifferentiates not only to cells derived from the paraxial mesoderm, such as an osteoblast, a chondrocyte, and an adipocyte, but also to cells derived from the splanchnic mesoderm, such as a vascular endothelial cell, a vascular smooth muscle cell, and a cardiomyocyte.

There have been almost no reports worldwide on the attempt in which cells obtained by using dedifferentiation culture technique, such as the preadipocyte cell line of the invention of the subject application, are used for regenerative medicine. The above-mentioned clinical application cases also indicate that the preadipocyte cell line used in the present invention is an epoch-making cell, and the method of independnent claim 15, and dependent claims 16-18, 23, 24, 29 and 30, wherein which a cell having other functions is acquired by using the preadipocyte cell line provides unpredictable, remarkable effects.

Therefore, PARK in view of LECOEUR and KANO fails to render obvious the claimed invention, and withdrawal of the rejection is respectfully requested.

Claims 15-19, 23-25, and 29-32 were rejected under 35 U.S.C. § 103(a) as being unpatentable over PARK in view of LECOEUR, KANO, ROSS, BENNETT and RANDO. This rejection is respectfully traversed for the reasons that follow.

BENETT use 3T3-L1 preadipocytes as preadipocytes (Experimental procedures, cell culture, P. 30999, Column 1). The 3T3-L1 cell line is a cell line produced by cloning a fibroblast derived from a fetus and is completely different from the preadipocyte cell line of the present invention in derivation.

Further, the 3T3-L1 cell undergoes differentiation induction into an adipocyte, but the adipocyte is different from an adipocyte collected from a living organism in characteristic, which has been proven by many researchers.

Therefore, it is impossible to conclude and is not obvious that the preadipocyte cell line of according the claims 15-19, 23-25, and 29-32 undergoes differentiation induction into a myoblast, because the pathway through which the 3T3-L1 cell line is converted to a muscle cell is the pathway which is connected to Wnt. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the amendment to claim 15 and the foregoing remarks, this application is in condition for allowance at the time of the next Official Action. Allowance and passage to issue on that basis is respectfully requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our credit card which is being paid online simultaneously herewith for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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RAM/dp

APPENDIX:

The Appendix includes the following items:

- EVIDENCE:

Nobusue and Kano, Journal of Cellular Biochemistry

9999: 1-11 (2009)